AD_________________

AWARD NUMBER: W81XWH-08-2-0188

TITLE: Disequilibrium after Traumatic Brain Injury: Vestibular Mechanisms

PRINCIPAL INVESTIGATOR: Mark Walker, M.D.

CONTRACTING ORGANIZATION: Case Western Reserve University
Cleveland, OH 44106

REPORT DATE: September 2009

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE
1 September 2009

2. REPORT TYPE
Annual

3. DATES COVERED
1 Sep 2008 – 31 Aug 2009

4. TITLE AND SUBTITLE

Disequilibrium after Traumatic Brain Injury: Vestibular Mechanisms

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-08-2-0188

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Mark Walker, M.D.

E-Mail: mark.walker@case.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Case Western Reserve University
Cleveland, OH 44106

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
The purpose of this study is to investigate mechanisms of disequilibrium and imbalance in veterans of Operation Enduring Freedom / Operation Iraqi Freedom who have experienced mild traumatic brain injury (mTBI). Chronic dizziness is a common symptom in these veterans and also in civilians after head injury, but the cause is not known. Our hypothesis is that damage to vestibular reflexes involving inner ear otolith organs (sensors of gravity and linear motion) and/or their brain connections are involved. To test this hypothesis, we are measuring vestibular and balance function in veterans with mTBI and comparing them to control subjects. In the first year of this study, we have set up our experimental protocols and have recruited and tested several subjects. Each of the two mTBI subjects that we have tested so far demonstrated otolith vestibulo-ocular reflexes that were lower than we have found in prior studies of normal subjects without vestibular problems. This finding is supportive of our hypothesis, but there are not yet sufficient data to make definitive conclusions.

15. SUBJECT TERMS
Traumatic brain injury, balance, locomotion, vestibular, eye movements

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U	UU	10	19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

TABLE OF CONTENTS

INTRODUCTION

The objective of this study is to investigate mechanisms of balance impairment in veterans of Operation Enduring Freedom / Operation Iraqi Freedom (OEF/OIF) who have experienced mild traumatic brain injury (mild TBI). Persistent disequilibrium is a known post-concussive symptom, and recent surveys of veterans have confirmed that this is also true of blast-related mild TBI (Cave et al. 2007; Scherer et al. 2007; Scherer and Schubert 2009). Prior studies in civilians have documented objective impairments in balance and locomotion, but the relationship of these deficits to vestibular injury has not been adequately studied. In particular, little is known about the effect of blast-exposure and mild TBI on the reflexes derived from the otolith organs of the vestibular labyrinth (the organs that respond to linear motion and sense gravitational acceleration). The hypothesis of this study is that impaired otolith reflexes account for persistent dizziness and gait impairment after mild to moderate traumatic brain injury. We are testing this hypothesis in a series of experiments designed to measure directly the otolith- and canal-mediated vestibulo-ocular reflexes and to correlate these to quantitative measures of static and dynamic balance and of walking. The results of this study will not only provide critical information regarding the pathophysiologic mechanisms of balance impairment after TBI, but they will also facilitate improved diagnosis of these problems in the acute and chronic settings.

Our effort in the first year of this study was focused first on finalizing human subjects approvals from our local IRBs (Cleveland VA Medical Center and University Hospitals and CDMRP), second on completing the implementation of our experimental protocols, and third on recruiting and testing initial subjects. Although we are somewhat behind our initial projections in terms of subject recruitment, we have made important progress in each of the first two aims outlined in the Statement of Work, and our initial data is very promising.

BODY

<u>TASK 1: VOR Measurements</u>

This task addresses Specific Aim 1: <u>Are vestibulo-ocular reflexes impaired in TBI subjects with disequilibrium</u>? We have recorded two mild TBI subjects and one normal subject. Measurements are performed on our Moog motion platform using scleral coils to record eye movements. Responses to horizontal and vertical linear translations and to horizontal rotations are recorded, along with saccades and pursuit eye movements. Our hypothesis predicts a specific deficit in translational vestibular responses, i.e. eye movements evoked by stimulation of the otolith organs.

In both TBI subjects recorded so far, the translational vestibulo-ocular reflex (TVOR) was less robust than in normal subjects. Note that although we have only recorded one normal subject for this study, we have TVOR data from a much larger number of normal subjects (Liao et al. 2008). The responses in our two TBI subjects were lower than any of these previously studied normal subjects (same task), as illustrated in Figure 1 for one of the two subjects. We quantify the TVOR by the compensation gain, which is the ratio of actual eye velocity to the calculated ideal eye velocity (the eye motion that would keep gaze on the target). The two mild TBI subjects had compensation gains of 0.23 and 0.34. In contrast to the TVOR, and in keeping with our hypothesis, both of these subjects had rotational responses within the generally normal range.

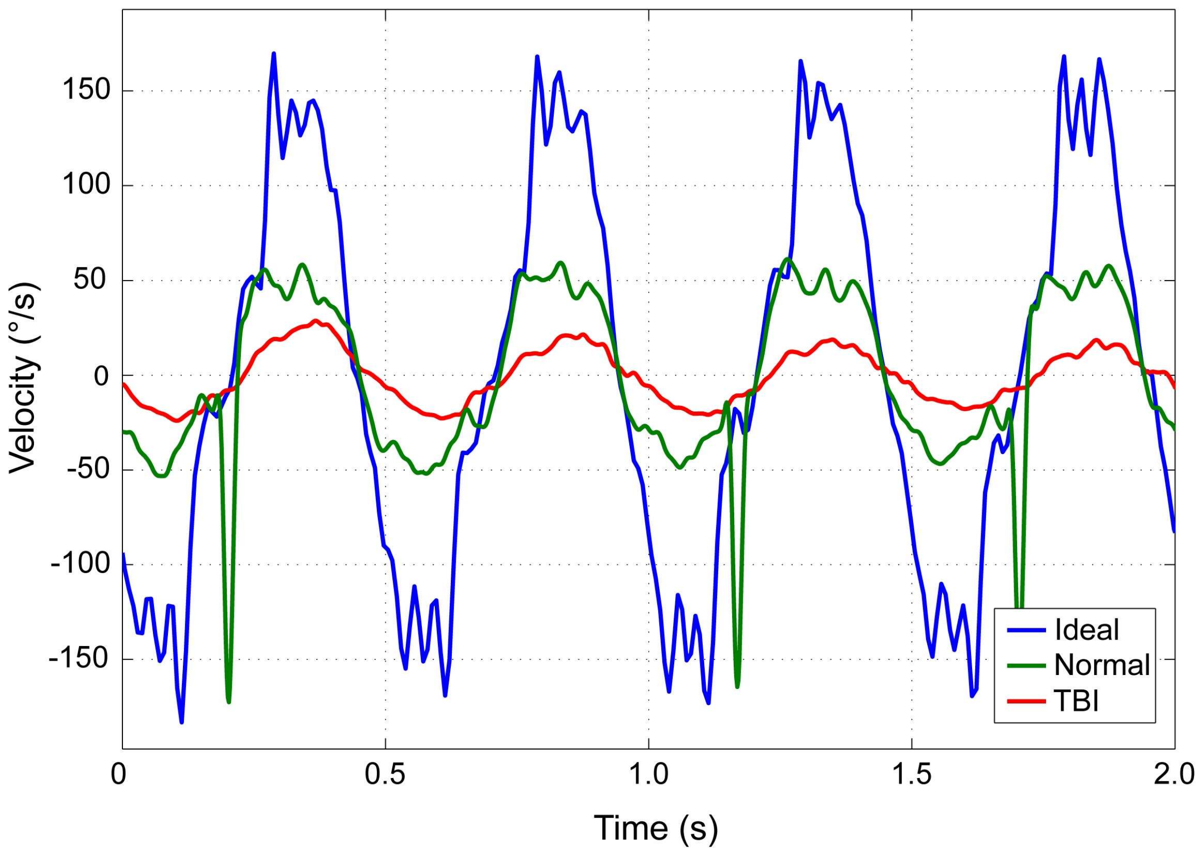

FIGURE 1: Horizontal eye velocity during side-to-side translational motion of the head and body on the motion platform (2 Hz). The blue line shows the ideal eye velocity, i.e., the motion of the eye that would keep the eyes fixed on the target (target distance 15 cm). The green trace shows recorded eye velocity in the normal subject, and the red trace shows eye velocity in the TBI subject. The TBI subject has a response that is less than half of the normal subject.

TASK 2: Gait and Balance Measurements

This task is performed in tandem with Task 1. Each subject in whom we record vestibular responses also undergoes testing of gait and balance function. Thus, we have also acquired these data in the same two TBI subjects and one normal subject. Unlike the TVOR, we do not have prior data in a comparison group of normal subjects, and thus the normal range is less clearly defined for these tasks. Nonetheless, there are key differences in the responses of the two TBI subjects from the normal subject, suggesting that these measures will be able to distinguish the two groups.

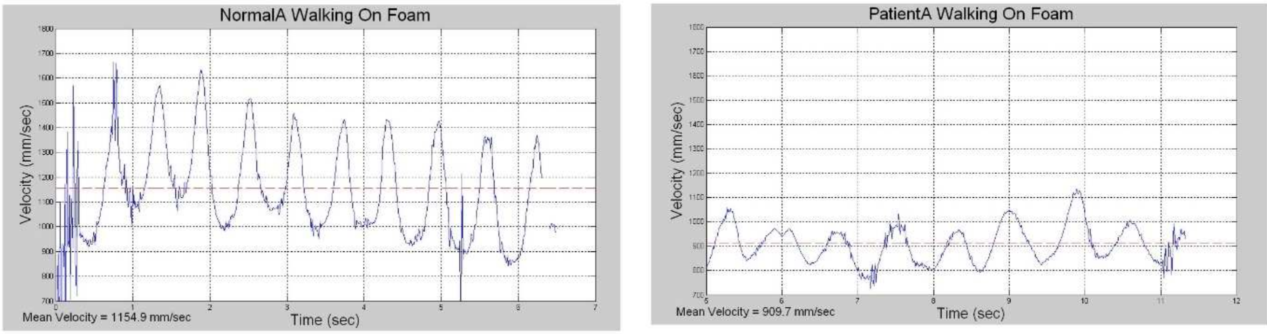

FIGURE 2: Forward velocity of the lower trunk (measured from an infrared-reflective marker at the waist level) during walking on foam in a normal subject and a subject with mild TBI. The scales of the two figures are identical to facilitate comparison. The dashed red line indicates mean gait velocity and the blue line instantaneous velocity. The normal subject walks faster and has a greater range of speed across each gait cycle.

Figure 2 shows instantaneous forward velocity in a normal subject and a TBI subject during walking on foam. Note that the normal subject has both a larger mean gait velocity and a greater variation of gait speed during each stride. The normal subject walks faster and more fluidly. Another measure of postural function is the ability to shift one's weight without falling over. Figure 3 compares trunk motion during voluntary weight shifting in one TBI subject and one normal subject. The subjects were instructed to lean forward and backward, as well as from side-to-side as far as they could without falling over. The TBI subject had more restricted movement. Finally, we test dynamic postural stability by measuring body motion in response to sudden forward or lateral pulls delivered by a linear actuator attached to a belt worn by the subject. Figure 4 shows the responses of one normal subject and one TBI subject in this task. The normal subject is better able to maintain his posture when perturbed.

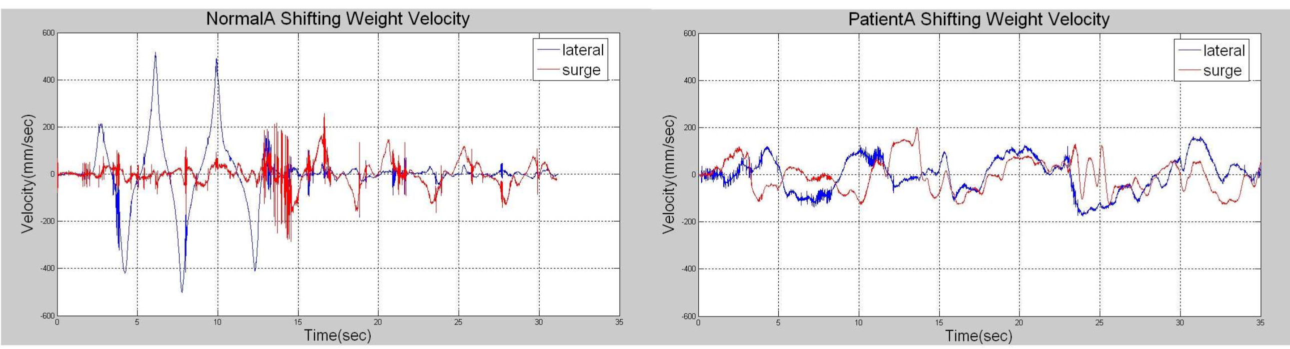

FIGURE 3: Velocity of voluntary weight shifting (measured from an infrared reflective marker at the waist) in the fore-aft (red) and side-to-side (blue) directions, in a normal subject (left) and a TBI subject (right).

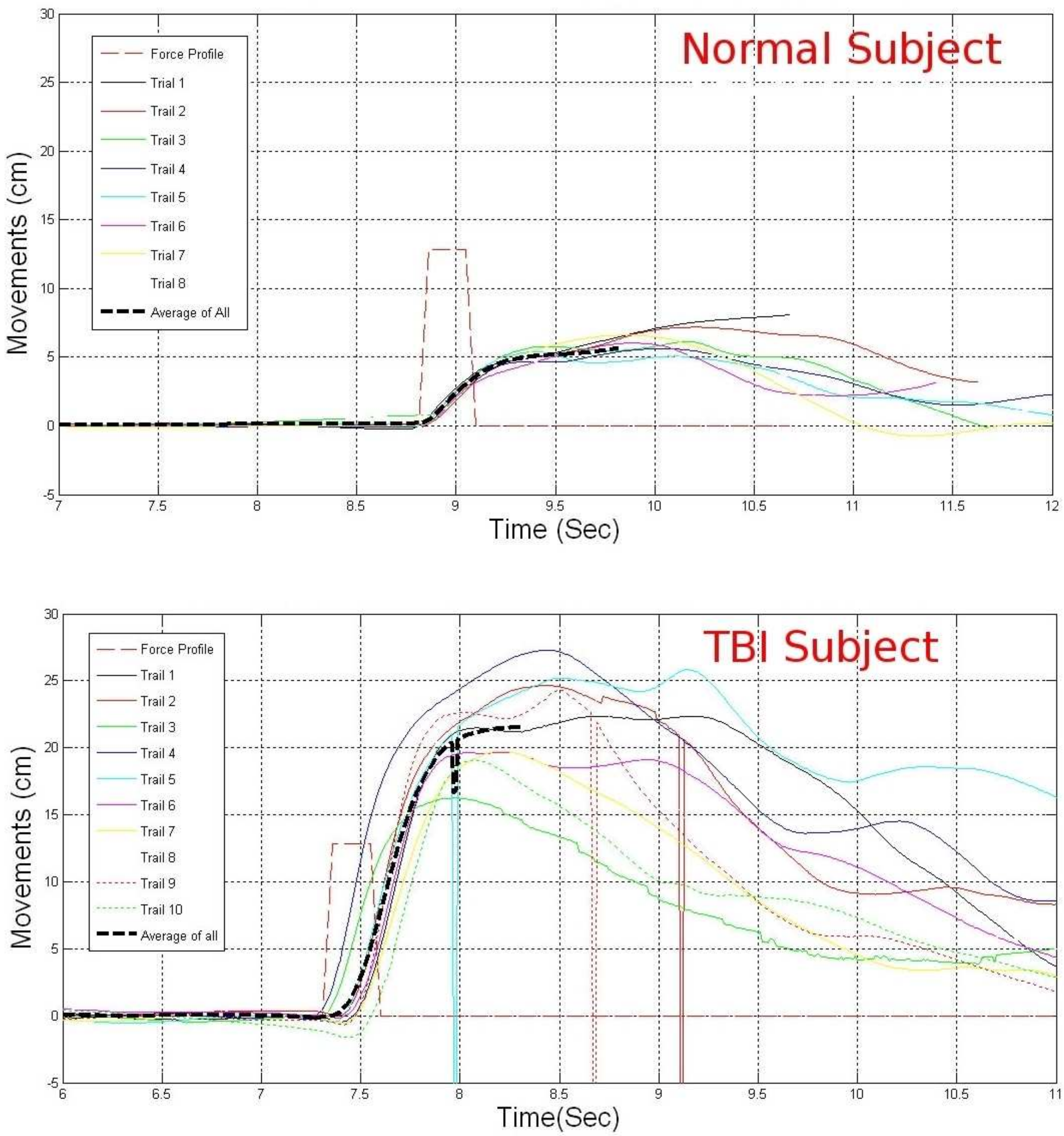

FIGURE 4: Responses to sudden forward postural perturbations in a normal subject (A) and a mild TBI subject (B). The kinematics of body motion are determined by a Vicon motion tracking system. The coarsely dashed red line shows the timing of the pull by the linear actuator, which is connected by a taut rope to a belt worn at the waist level. Each colored trace represents the linear position of the lower trunk (calculated average motion of three reflective markers positioned around the waist). Positive movement is in the direction of the pull. Note that the normal subject has stabilized his posture by the time the pull stops, whereas the TBI subject continues to move forward. As a consequence, the total forward displacement of the TBI subject is about four times greater than that of the normal subject.

TASK 3: VOR Adaptation / Motor Learning

This task has not yet commenced, according to the plan outlined in the Statement of Work. This is intended to be the final experiment of this project.

KEY RESEARCH ACCOMPLISHMENTS

We have not completed recruitment and testing of subjects. Thus, it is not possible to make definitive conclusions from our data. At this stage, the key accomplishments are:

•We have successfully recorded ocular responses to translational motion in three subjects. As far as we know, this is the first time these important vestibular reflexes have been studied in any subjects with TBI, whether due to blast-related or blunt head trauma.

•We have implemented our protocol for testing gait and balance, and we have successfully recorded data from these same three subjects. We have made substantial progress in the development of software tools to analyze these data.

•Our preliminary data, although inconclusive at this point, support our hypothesis and indicate that it is likely that we will be able to make meaningful distinctions between veterans with mild TBI and control subjects.

REPORTABLE OUTCOMES

Preliminary data from this experiment were presented in poster form and in a platform session at the Military Health Research Forum, August 31 to September 3, 2009, Kansas City, MO (see Appendix).

CONCLUSION

This study will provide critical new information regarding the effect of mild TBI on vestibular function and the relationship of vestibular impairment to gait and balance problems. Although limited data preclude making conclusions at this stage, our preliminary results are promising and generally support our hypothesis. The findings from this study will be important for increasing our understanding of the nature and mechanisms of combat-related traumatic injury, for improving diagnostic techniques, for assessing functional impairment related to vestibular injury (which could be important for determining a veteran's capacity for performing duties that may depend on robust balance), and, finally, for refining rehabilitative strategies.

REFERENCES

Cave KM, Cornish EM and Chandler DW. Blast injury of the ear: clinical update from the global war on terror. *Mil Med* 172: 7: 726-730, 2007.

Liao K, Walker MF, Joshi A, Reschke M and Leigh RJ. Vestibulo-ocular responses to vertical translation in normal human subjects. *Exp Brain Res* 185: 4: 553-562, 2008.

Scherer M, Burrows H, Pinto R and Somrack E. Characterizing self-reported dizziness and otovestibular impairment among blast-injured traumatic amputees: a pilot study. *Mil Med* 172: 7: 731-737, 2007.

Scherer MR and Schubert MC. Traumatic brain injury and vestibular pathology as a comorbidity after blast exposure *Phys Ther* 89: 9: 980-992, 2009.

APPENDIX

Abstract

Military Health Research Forum 2009, Kansas City, MO

Vestibular Mechanisms of Imbalance after Traumatic Brain Injury

Mark Walker

Case Western Reserve University

Background and Objectives: Disequilibrium and imbalance are common problems after military and civilian TBI, but little is known regarding the underlying mechanisms of these problems, how best to measure them, and what the most effective treatments are. Prior reports indicate that 12% to 15% of soldiers with blast exposure will have chronic dizziness (Scherer, et al., 2007; Cave, et al., 2007), and this can persist months or years after the acute injury. These problems are important, because they can interfere with an individual's ability to return to work (Hoffer, et al., 2004) or combat. In civilians with mild blunt TBI, walking speed and stability are reduced (Basford, et al., 2003), and these impairments correlate with subjective disequilibrium (Kaufman, et al., 2006). Despite the importance of gait and balance deficits after TBI, the mechanism of injury underlying them remains unknown. Our hypothesis is that impairment of otolith-mediated vestibular reflexes play a central role. We are testing this hypothesis by performing a detailed assessment of vestibular function, gait, and balance in three groups of subjects: (1) OIF/OEF Veterans with a history of blast-induced mild TBI (mTBI) and chronic disequilibrium, (2) OIF/OEF Veterans with a history of mTBI but no disequilibrium, and (3) non-Veterans with no history of TBI or vestibular symptoms. In our clinical practice, we have already identified a number of Veterans with disequilibrium, and many of these demonstrate objective abnormalities on clinical posturography testing that support our hypothesis.

Methods: To assess the integrity of otolith reflexes, we will measure the translational vestibulo-ocular reflex (TVOR, eye movements generated in response to linear motion of the head and body) on a computer-controlled motion simulator platform equipped with a magnetic-field search coil eye movement recording system. In our laboratory, we have used this method to identify critical otolith reflex impairments in individuals with other neurological diseases that cause imbalance, such as cerebellar ataxia and progressive supranuclear palsy. In the same subjects, we will measure head, limb, and body kinematics and EMG during gait and balance tasks. We will compare results among groups and, in subjects with disequilibrium, we will correlate gait and balance with TVOR measures.

Potential Impact: This study will yield important new information regarding the mechanism of imbalance in veterans that have suffered blast-induced TBI. We anticipate that our data will help to improve clinical diagnosis and assessment of these problems and will lead to better treatment strategies.

This work was supported by the U.S. Army Medical Research and Materiel Command under W81XWH-08-2-0188 and Department of Veterans Affairs.